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学位授与の題目	Experimental Study to Elucidate the Origin of "Syn-Effect" （「シン効果」の本質解明を目指した実験的研究）
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学位論文要旨

Abstract

It was found that $\sigma\rightarrow\pi^*$ interaction is the most probable origin of the "*syn-effect,*" observed in the conversion of (*E*)-α-fluorovinylic sulfones to the corresponding allylic sulfones. Also, in the isomerization reaction of (*E*)-α,β-unsaturated esters and in the conversion of aldehydes into silyl enol ethers, $\sigma\rightarrow\pi^*$ interaction was found the most important factor to determine the relative degree of *"syn-effect."* Based on these observations, *"syn-effect"* was investigated under enhanced $\sigma\rightarrow\pi^*$ interaction in the desilylation reaction of γ-silylated allylic and vinylic sulfones. A new result was also observed for the reaction of dienyl sulfone with various nucleophiles, where the unexpected (*Z*)-addition product was obtained as the major product.

The synthetic utility of allylic and vinylic sulfones is now well recognized. The paramount importance of the allylic sulfones is the ease of formation of carbanions α to the sulfonyl group. This enables efficient C–C bond formation via alkylation, acylation, and aldol-like reactions. Also, the sulfonyl group of allylic sulfones can act as a leaving group in substitution reactions or elimination reactions. Vinylic sulfones have now become generally accepted not only as useful intermediates in organic synthesis, but also as precursors of the corresponding allylic sulfones.

The previous reports from our laboratory revealed the stereochemistry of the conversion of vinylic sulfones to the corresponding allylic sulfones by treatment with a base under mild conditions, that is, (*E*)-vinylic sulfones preferentially afforded (*Z*)-allylic sulfones as kinetically controlled products, while (*Z*)-vinylic sulfones and α-alkylated vinylic sulfones gave (*E*)-allylic sulfones exclusively. The former

experimental results were rationalized by a new concept "*conformational acidity*" (a sort of kinetic acidity) which essentially implies the "*syn-effect*" ("*syn-effect*" is defined here as an effect which stabilizes the *syn*-conformation against the steric hindrance).

Besides the 6π-electron homoaromaticity, $\sigma \rightarrow \pi^*$ interaction was proposed as another probable origin of the "*syn-effect.*"

In order to find out the exact origin of "*syn-effect*", firstly, the hydrogen atom at the α-position of (*E*)-vinylic sulfones was replaced by a fluorine atom, as its size is not so much different from that of hydrogen, and extra unshared pair of electrons exists on the fluorine atom to avoid 6π-electron homoaromaticity by the formation of 8π-electron system in *syn*-transition state (Figure 1).

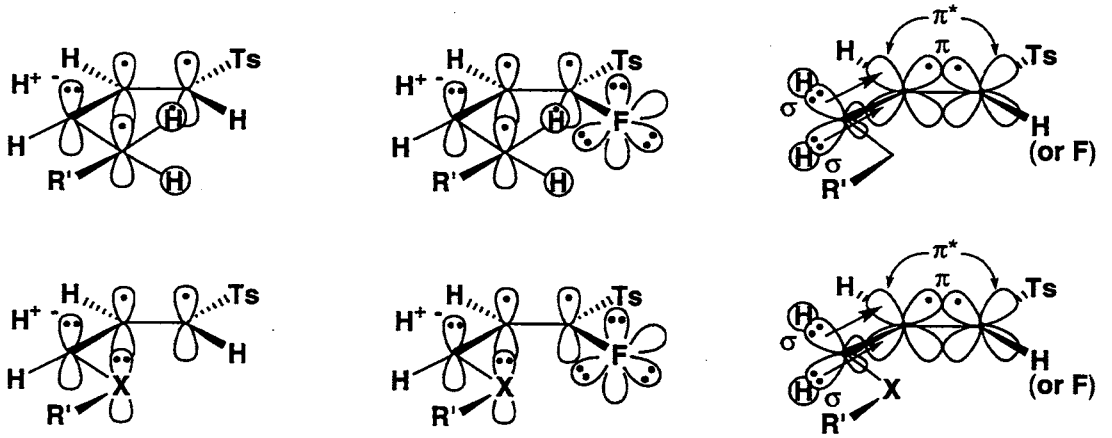
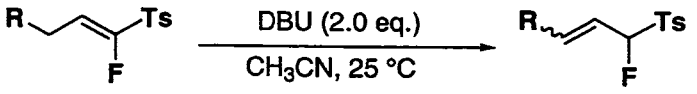


Figure 1.

After preparing (*E*)-α-fluorovinylic sulfones bearing various substituents at the γ-position, their conversion to the corresponding allylic sulfones have been investigated by treatment with a base under mild conditions. In order to reveal the stereochemical relationship, time course of the reactions were also observed in every cases.



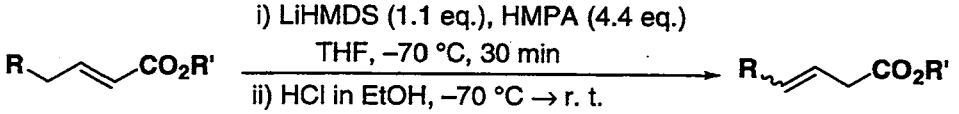
As mentioned above, the concept of 6π-electron homoaromaticity is not applicable in the present case. However, we could still observe the "*syn-effect*" especially in the conversion of γ-fluorinated (*E*)-α-fluorovinylic sulfones to the corresponding allylic sulfones. Therefore, in this case the "*syn-effect*" is arising from the interaction between the σ-orbital of the allylic C-H bond(s) and the *anti*-bonding orbital (π^*) of the C=C double bond, namely, the $\sigma \rightarrow \pi^*$ interaction in the transition state (Figure 1). The

relative degree of the "*syn-effect*" for various γ-substituents of (*E*)-α-fluorovinylic sulfones in their conversion to the corresponding allylic sulfones was found as follows:

$$F- > EtO- > CH_3- > BnS- > CH_3CH_2- > (CH_3)_2CH- > (CH_3)_3C-, Ph-$$

Fluorine atom showed the highest "*syn-effect*" among the substituents investigated. The relative degree of "*syn-effect*" for other substituents remains the same as found in the conversion of α-unsubstituted (*E*)-vinylic sulfones to the corresponding allylic sulfones.

Next, the stereochemistry in the isomerization reaction of (*E*)-α,β-unsaturated esters to the corresponding β,γ-unsaturated esters under basic conditions was investigated.

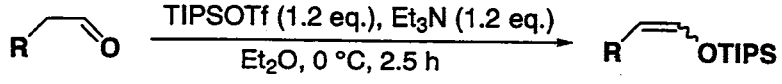


The relative degree of "*syn-effect*" for various substituents at the γ-position was found to follow the order:

$$F- \approx BnO- > CH_3- > CH_3CH_2- > PhCH_2- > (CH_3)_2CH- > PhS- > BnS- > (CH_3)_3C- > Ph-$$

In this case, almost the same result was observed as in the conversion of (*E*)-α-fluorovinylic sulfones to the corresponding allylic sulfones except benzylthio and phenylthio groups. The latter exception probably due to the difference between the present electron deficient conjugated olefinic system and the non-conjugated olefinic system in vinylic sulfones. Fluorine atom and benzyloxy substituents showed the highest "*syn-effect.*"

Furthermore, the stereochemistry in the conversion of aldehydes into silyl enol ethers was investigated. Various α-substituted aldehydes were converted to the corresponding silyl enol ethers by treating with a silylating agent in the presence of a base.



It was found that α-benzyloxy group showed the highest (*Z*)-selectivity. The *Z*/*E* ratios of the resulting silyl enol ethers were dependent on the α-substituents of the aldehydes. These results were also well explained on the basis of "*syn-effect*" which was mainly arisen from the $\sigma \rightarrow \pi^*$ interaction and/or 6π-electron homoaromaticity.

It should be noted that in the present investigation, the (*Z*)-selectivity of the silyl enol

ethers obtained in the reaction utilizing silyl triflate was higher than the result obtained in the reaction using silyl chloride. This is because, by using stronger lewis acid, silyl triflate, as the silylating agent, the activation energy of the reaction was decreased by lowering the energy level of the π^* orbital. Under these conditions, $\sigma \rightarrow \pi^*$ interaction could work more effectively and as a result, the (*Z*)-selectivity increased (Figure 2).

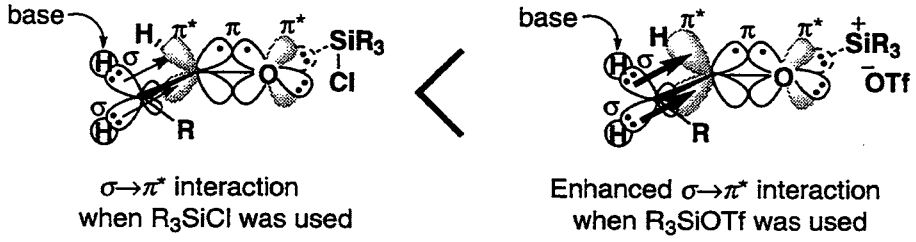
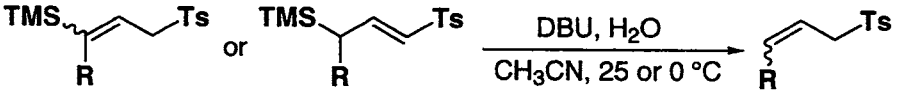


Figure 2.

It is well known that the hyperconjugative electron donation ability of C–Si bond is stronger than either C–C or C–H bond. In order to observe the enhanced effect of $\sigma \rightarrow \pi^*$ interaction on *"syn-effect,"* one hydrogen atom at the γ-position of allylic and vinylic sulfones was replaced by a trimethylsilyl (TMS) group. Various γ-silylated allylic and vinylic sulfones were synthesized in different routes to investigate the stereochemistry of their desilylation reaction with DBU and H_2O.



The *Z*/*E* ratios of the resulting desilylated allylic sulfones were found to be independent on the stereochemistry of the starting γ-silylated allylic sulfones, which suggested that desilylation did not occur directly from the γ-silylated allylic sulfones. Recovery of the γ-silylated vinylic sulfone from γ-silylated allylic sulfone in the case of *tert*-butyl substituent, and the unreactivity of γ-methoxy substituted γ-silylated allylic sulfone revealed that the reaction proceeded through γ-silylated (*E*)-vinylic sulfones. The relative degree of *Z*/*E* ratio in the desilylation reaction depending on the γ-substituents of silylated sulfones was found to follow the order:

$$CH_3O\text{-} > CH_3\text{-} > CH_3CH_2\text{-} > PhCH_2\text{-} > NC\text{-} > PhS\text{-} > (CH_3)_2CH\text{-} > Ph\text{-} > (CH_3)_3C\text{-}$$

In the present reaction, the (*Z*)-selectivity was higher than that of the previous rearrangement of γ-unsilylated (*E*)-vinylic sulfones to the corresponding allylic sulfones as expected, except the case of ^{i}Pr group probably due to the steric demand. These results were also well discussed by the *"syn-effect,"* which is primarily rationalized by

$\sigma \rightarrow \pi^*$ interaction.

On the other hand, when the desilylation reaction was carried out by using $^nBu_4NF$ instead of DBU and H_2O under similar conditions, the (*Z*)-selectivity was lower even though the reaction proceeded much faster. Based on this observation, it could be concluded that more basic conditions are favorable to discriminate the conformation **B** from **C** (Figure 3).

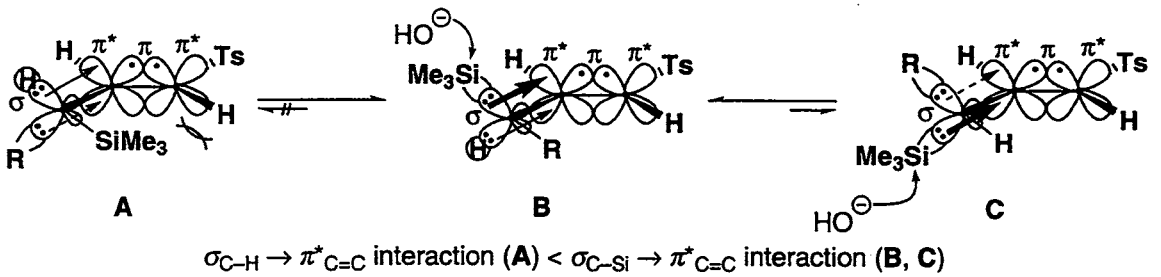
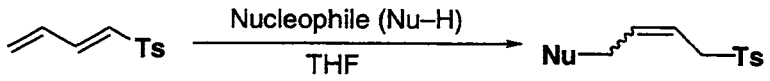


Figure 3.

Finally, the reactions of dienyl sulfone with various nucleophiles were investigated. It was found that the products obtained from the reaction of (*E*)-1-tosyl-1,3-butadiene and dialkylamine of linear alkyl chain groups (either symmetric or asymmetric) preferred (*Z*)-selectivity.



The (*Z*)-selectivity in THF was found to be higher than that of diethylether or bezene. Whether this (*Z*)-selectivity is due to the 1,4-addition of the nucleophile to the *syn*-conformation of (*E*)-1-tosyl-1,3-butadiene, or due to the stability of the intermediary zwitter ion species derived from the *syn*-conformation of dienyl sulfone, or due to other reasons, is not clear yet. In order to find out the exact origin of this unexpected (*Z*)-selectivity, the related works are now in progress.

学位論文審査結果の要旨

本学位論文に対して、各審査委員が参考論文等の関連資料を含めた予備審査を行い、さらに平成16年2月10日の口頭発表における質疑応答（最終試験に代える）の結果を踏まえ、同日開催された審査委員会において以下の通り判定した。

本論文は、α－無置換ビニル型スルホンのアリル型スルホンへの異性化反応において見出された、立体障害の概念に反する興味深い現象である「シン効果」の本質解明を目指して、(1) α－フルオロビニル型スルホンのアリル型スルホンへの異性化反応、(2) α，β－不飽和エステルのβ，γ－不飽和エステルへの異性化反応、(3) α－置換アルデヒドのシリルエノールエーテル化反応、(4) γ－シリル置換型アリルあるいはビニル型スルホンの脱シリル化反応、の立体化学について、γ－あるいはα－置換基依存性を中心に実験的に詳細に検討した結果について述べている。即ち、これまで「シン効果」の原因として考えられていた6π電子系のhomoaromaticityとσ→π*相互作用のうち、σ→π*相互作用が「シン効果」の主な原因であることを明らかにするとともに、「シン効果」は、電子不足型sp^2炭素に隣接するアルキル基に本来備わっている一般的な現象であることを明らかにした。

これらの有機立体化学に大きく貢献する注目すべき成果は、博士（理学）の学位を与えるに充分値するものであると判定した。